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EXAMINER	
MYERS, CARLA J	

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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,500	VAN BROECKHOVEN ET AL.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

nDETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 3, 2006 has been entered.

Claims 1-5 are pending and have been examined herein. The previous rejection of claims 1-5 under 35 USC 112, second paragraph is withdrawn in view of the amendment to the claims. The following includes new grounds of rejection and is made non-final.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the

nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to method for identifying a human coding region/gene, including mutated and polymorphic variants thereof, which are associated with a bipolar disorder, comprising identifying the position of a coding region or gene between the markers D18S68-D18S979, comparing the sequence of this region or gene from a person affected with bipolar disorder with that of a control individual, and detecting differences in the sequence of the coding region or gene present in said individual wherein any difference in the coding region or gene identifies a coding region or gene or mutated or polymorphic variant associated with the mood disorder or related disorder. The claims as broadly written encompass:

a) identifying novel coding regions, genes, mutations and polymorphisms associated with bipolar I or bipolar II type disorders.

b) methods of searching for known or unknown coding regions and genes and for mutations and polymorphisms in the 9.8cM region between the markers D18S68 and D18S979 (i.e., a region of approximately 8.9 million base pairs) or a region between markers D18S60 and D18S61 (a region of about 15.2 cM or 15.2 million base pairs; see pages 6 and 28 of the specification) and trying to establish a correlation between these

regions/genes, mutations and polymorphisms and the occurrence of any mood disorder or related disorder.

Nature of the Invention

The claims are drawn to methods for detecting a coding region or a gene or a mutation or polymorphism therein by assaying for the presence of genetic variation between markers D18S68 and D18S979. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

The specification teaches that a susceptibility locus for bipolar disease had been previously identified within the region of 18q21-q23 (page 4). The specification (page 24-25) provides the results of a study from a Belgian family (MAD31) having a BPII proband wherein the susceptibility locus was refined to include a region of 8.9 cM located between the 18q markers D18S68 to D18S979. It is stated that this region may now be "used to locate, isolate and sequence a gene or genes which influences psychiatric health and mood" (page 5). Further, "once candidate genes have been identified it is possible to assess the susceptibility of an individual to a mood disorder or related disorder by detecting the presence of a polymorphism associated with the mood disorder or related disorder in such genes."

The specification teaches multi-linkage analysis of STRs located between the markers of D18S51 and D18S61 for cosegregation with bipolar II disease in family MAD31. The results of LOD score analysis is set forth in Table 2 (page 31). The highest individual LOD score obtained for any marker was 2.01. However, as set forth on page 4 of the specification, "A LOD score of 3 (or likelihood ratio of 1000 or greater) is taken as significant statistical evidence for linkage."

The results set forth in the specification indicate that several of the markers in the claimed region were determined by Applicants to NOT be significantly linked to BPII. For instance, for "Model 1," the following markers in this region did not have lod scores that would be viewed as significant: the lod score for D18S68 and D18S346 was –0.19; the lod score for D18S969 was 1.40; the lod score for D18S979 was –0.18; the lod score for D18S61 was –0.21. That is, the claims include the analysis of the region between markers D18S68 to D18S113. However, Applicant's data establishes that the markers in this region, namely D18S68, D18S346 and D18S969 were not linked with BPII. Further, the claims encompass the analysis of a region that spans markers D18S79 to D18S61. However, the markers in this region, D18S979, D18S817 and D18S61 had lod scores of –0.18, -0.19, and –0.21, respectively and thus were not linked with BPII in this proband. Further, no data is provided for the markers between D18S60 and D18S68 or between D18S61 and D18S979. The specification (e.g., Figure 14) discusses only the region between D18S68 and D18S979 as being a "BP candidate region." There is no evidence to support the conclusion that the regions outside of D18S68- D18S979, extending to D18S61 and D18S60 are associated with BP.

The specification does not disclose a single gene or coding region within the region of D18S68-D18S979. Further, the specification does not disclose any particular mutations or polymorphisms within the region of D18S68-D18S979 which are associated with BP II. Moreover, the specification does not provide any results regarding the linkage of the D18S68-D18S979 markers or other markers within this region and the occurrence of other bipolar disorders.

The Predictability or Unpredictability of the Art and Degree of Experimentation:

The art of identifying genes associated with a disease and detecting the presence of novel mutations associated with the occurrence of disease is highly unpredictable. Once a region associated with a gene is known, extensive experimentation remains to determine which, if any, genes within this region are sufficiently linked to a disease in order to allow for diagnosis of the disease by detecting the gene. Further, once a gene associated with a disease is identified, significant experimentation is also required to identify particular mutations and polymorphisms within that gene which are diagnostic of disease. The identity of the gene/coding region and the identity of the mutations and polymorphisms are the novel features required to practice the claimed invention. However, the specification does not teach the structural and functional properties of the coding regions/genes or mutations/polymorphisms. Rather, the specification outlines the methodology by which a researcher could perform extensive, trial-by-error experimentation in order to try to identify genes/coding regions and mutations/polymorphisms which could be used within the claimed methods. Disclosure of a 8.9 cM region linked to BPII is not equivalent to disclosing specific

genes/coding regions and nucleotide variations which are associated with BP or other mood related disorders. To identify genes or mutations within this 8.9 cM region requires significant experimentation in which researchers may be required to create a clonal library containing candidate cDNAs which would then be sequenced and compared to nucleic acid databases to identify a gene or genes which may constitute the bipolar susceptibility gene. The cDNAs identified that map to the minimal candidate region would then used as probes to screen a contig library. This screening then identifies new markers which are used to genotype the linkage disequilibrium sample. The cDNAs identified by these screens are then used to screen patient DNA for mutations and polymorphisms associated with bipolar disorders. Such random, trial-by-error experimentation is considered to be undue.

The art corroborates the unpredictability in identifying polymorphisms and mutations associated with BP and in identifying a specific loci within chromosome 18 that is definitively associated with BP. For example, McInnes (Proceedings of the National Academies of Sciences, USA. November 1996. 93: 13060-13065) teaches that interpreting results form linkage analysis of bipolar mood disorder and other behavioral phenotypes is very difficult and often misleading because behavioral phenotypes are difficult to define, as they are etiologically heterogeneous and there is a lack of knowledge as to the mode of transmission of these diseases. McInnes concluded that it is unlikely that any one linkage study will yield sufficient evidence to localize a gene for any psychiatric disorder (page 13060, col. 2, paragraph 1). McInnes performed a genome screening analysis for possible genes associated with BP and found

suggestive lod scores in segments 18q, 18p and 11p. McInnes teaches that genome screening is the first step of a multi-step process for identifying genes for complex traits and that several additional steps and experiments would be required to delineate a clear candidate region (page 13064, col. 2). Gerson (Neuropsychopharmacology. 1998. 18: 232-242) reviewed the progress in identifying genes associated with manic-depressive illness and concluded that while chromosome 18, and particularly the short arm of chromosome 18, is one of the best candidate locations for a bipolar susceptibility gene, and that the positive linkage results represent important progress, scientists are still a long way from demonstrating a disease mutation correlated with bipolar illness (page 239, col. 2). Nothen (Molecular Psychiatry. 1999. 4: 76-84) concluded that as late as 1999 that the data in the art supports the hypothesis that a susceptibility locus exists and may specifically exist on chromosome 18, but does not provide a reasonable expectation that polymorphisms in the region of 18q are associated with a bipolar susceptibility locus or what that locus will be. Nothen (page 82) states that "(a)ny single study will be insufficient to provide convincing proof for a susceptibility locus in a complex disease because of unknown mode of inheritance, genetic heterogeneity, and nongenetic factors."

The teachings of Lucentini (The Scientist. December 2004, page 20) further highlight the unpredictability in the art of establishing an association between a mutation/polymorphism and the occurrence of a disease or condition. As discussed by Lucentini, reproducible association studies are "few and far between." The reference reports that "when a finding is first published linking a given gene with a complex

disease, there is only roughly a one third chance that studies will reliably confirm the finding. When they do, they usually find the link is weaker than initially estimated. The first finding is usually 'spurious, or it is true, but it happens to be really exaggerated, ' ...there may be no way to predict which new gene-association studies will be verified with multiple replication."

The teachings of Goossens et al (European Journal of Human Genetics, 2000; of which 2 of the present inventors are co-authors) also supports the unpredictability in the art. In this post-filing date reference, the authors report that no association was found between triplet repeats in the 18q21.33-q23 region and bipolar disease family MAD31 and 75 unrelated BP cases (see page 388). With particular respect to claims 7, 9,10, 20, 26 and 27, the specification and prior art do not teach any particular trinucleotide repeats in the regions between D18S60-18S61 or D18S68-D18S979 whose presence is indicative of a coding region or gene or mutated or polymorphic variants thereof associated with mood disorders or related disorders.

The teachings of the post-filing date art of Del-Favero (WO 02/101044; cited in the IDS; of which 2 of the present inventors are co-inventors/applicants) also supports the unpredictability of identify a gene or mutation associated with BP. Del-Favero teaches that a gene, NCAG1, identified in the presently claimed region, contained 2 polymorphisms, but neither polymorphism was associated with BP. The reference (page 17) states that "(n)o alleles, genotypes, or haplotypes were found to be associated with BP disorder."

Further, it is highly unpredictable as to whether the linkage results obtained with family MAD31 would be applicable to other bipolar disorders (e.g., BP-I, SAD-M, and unipolar major depressive disorder). The different types of bipolar disorders are believed to be genetically distinct. These disorders also have different symptomologies. No evidence or scientific arguments have been presented to establish that the results obtained with one family having a BPII proband can be extrapolated to all other types of bipolar disorders. The unpredictability of extrapolating the results obtained with the MAD31 family to other bipolar disorders is supported by the teachings of De bruyn (Biological Psychiatry. 1996. 39: 679-688; cited in the IDS). This reference reports that no linkage was observed with the 18q markers in a MAD22 Jewish Ashkenazi family of BPI proband (see pages 680 and 683).

Amount of Direction or Guidance Provided by the Specification:

The specification does not provide any specific guidance as to how to predictably identify a coding region / gene or mutation / polymorphism in the D18S68-D18S979 or D18S60-D18S61 region which is associated with and can be used to diagnose a mood disorder or a related disorder. While methods for performing linkage analysis and for sequencing genes and comparing the sequence of genes from patients and control individuals are known in the art, such methods provide only the general guidelines that allow researchers to search for novel genes and mutations. Providing methods for searching for a gene or mutation is not equivalent to teaching specific genes and mutations associated with mood disorders and related disorders. Even by following the method steps set forth in the present claims, one would not arrive at coding

regions/genes or variants thereof that are associated with mood disorders. The mere presence of a genetic variation between the DNA of one affected person and the DNA of one control person does not alone indicate that the variation is associated with a disorder, since many of the variants will not be specific to the affected individuals. That is, the variants are equally likely to represent polymorphisms present in the general population and not specifically associated with a mood disorder in the general population.

The teachings in the specification do not provide a reasonable expectation that one of skill in the art can identify variants associated with bipolar mood disorder or can identify a bipolar susceptibility locus without undue experimentation because of the high level of unpredictability in the art (as discussed above) and because the specification has not provided evidence that would allow the skilled artisan to predict the location and identity of specific bipolar susceptibility genes and mutations / polymorphisms. The specification presents data defining a smaller region of the 18q arm which has a higher probability of containing a susceptibility locus, but as of 1999, the art indicates that scientists are a long way from pinpointing specific genes, polymorphisms and mutations that are associated with bipolar disease or related disorders. The specification describes a research project for searching for genes and mutations that may exist in the defined region but the protocol described constitutes undue experimentation because the skilled artisan would be required to perform a large amount of essentially random screening of the defined region and would not be able to reasonably predict from the specification the identity of the gene or mutations

associated with BP. Furthermore, the claims as written are directed to a research project without a predictable outcome because they encompass methods which detect novel bipolar disease susceptibility genes and polymorphisms. The art makes clear that this objective is of great interest and the target of extensive research by many groups. In fact, many groups have taken the same approach as described in the specification for identifying such a bipolar locus without success. The specification essentially suggests that the artisan should analyze all possible mutations or polymorphisms within the 8.9 million bp region of D18S to D18S979 and then determine which variations within this region represent mutations or polymorphisms that could be used to diagnose a mood disorder. Such experimentation is considered to be undue.

Working Examples:

The specification does not provide any working examples of methods in which a coding region / gene or mutated or polymorphic variant thereof is identified and wherein the coding region / gene or variant is associated with mood disorder or any other related disorder.

Conclusions:

Case law has established that "(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of

guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that "(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement". In the instant case, the claims do not bear a reasonable correlation to the scope of enablement because the specification does not teach a single coding region or gene or variant thereof which is associated with a bipolar disorder. The specification does not provide the novel aspects of the claimed invention because the disclosure of a 8.9 cM region linked to BPII is not equivalent to teaching specific sequences that constitute coding regions / genes or mutations that are associated with a BP disorder. The specification provides the researcher with only an invitation to experiment and to try to find a new gene or mutation that is associated with mood disorder and which could be used to diagnose a bipolar disorder. No specific guidance is provided as to what would be the identity of such a gene or mutation / polymorphism. Accordingly, given the high level of unpredictability in the art and the lack of specific guidance provide in the specification and prior art, it would require undue experimentation for one of skill in the art to practice the claimed invention.

RESPONSE TO ARGUMENTS:

In the response filed July 3, 2006, it is stated that "Applicants are not claiming to have identified specific genes or coding regions, but based on discovering that a region of DNA is associated with bipolar disorder, are claiming methods to identify such one or more coding regions or genes associated with bipolar disorder."

This argument has been fully considered but is not persuasive. The claims are drawn to methods for identifying a gene or coding region, or a mutated or polymorphic variant thereof, which is associated with a bipolar disorder. The identification of such a gene, mutation or polymorphism is accomplished by comparing a sequencing within the 8.9 cM region D18S68 to D18S979 or the 15.2 cM region D18S60-D18S61 of a person afflicted with a bipolar disorder to an equivalent region of human DNA (the source of which is undefined). The presence of any sequence difference within these regions is interpreted as indicating the presence of a coding region or gene or a mutation or a polymorphism that is associated with a bipolar disorder. However, those of skill in the art would not interpret the results obtained by comparing one afflicted individual's DNA to an unstated source of DNA as indicating the presence of a gene, coding region, mutation or polymorphism associated with bipolar disorder. The comparison of the DNA sequences between one individual with bipolar disorder to the DNA sequences of another sample would not provide meaningful results that would allow one to draw a conclusion that the identified sequence difference was associated with bipolar disorder since the identification of a mutation or polymorphism associated with a disorder can only be ascertained by determining that the mutation or polymorphism is present in a statistically significant number of afflicted individuals and that the mutation or polymorphism is absent in normal, control individuals which are representative of the general population. Polymorphisms occur throughout the human genome at a frequency of one out of about every 100 to 300 bases. Those of skill in the art would recognized that not all polymorphisms present between D18S68-D18S979 or D18S60-D18S61 will

be linked to bipolar disease. Thereby, it is clear that the sequence comparison step alone does not identify a mutation or polymorphism associated with bipolar disorder. The identity of a polymorphism which would be linked to bipolar disorders can only be ascertained through extensive trial-by-error experimentation. The claims as written set forth the first steps of a research project. The results of this research project do not in fact identify a gene, mutation or polymorphism associated with bipolar disorder. Rather, the identification of a difference in the sequences provides a starting point for researchers to begin investigating the sequence difference to determine its association with a bipolar disorder.

Applicants assertion that the claims do not require specific genes or coding regions is unclear. The claims require the first process step of "identifying the position of a coding region/gene in an 8.9cM region of human chromosome 18q." One cannot identify the position of a coding region or gene without having knowledge of the identify of the coding region or gene. Thereby, the claims do in fact require that the skilled artisan use a specific coding region or gene. To practice the claimed invention requires knowledge of and identification of a specific gene or coding region – this requirement is not removed by the fact that the claim is drawn to a method or that the claim fails to recite the identity of the gene. Yet, the specification does not disclose any particular genes or coding regions in the stated 18q region and for the reasons stated above, it would require extensive experimentation to identify a novel gene within the 8.9 million base pair region between D18S68-D18S79 or between the 15.2 million base pair region between D18S60-D18S61.

The response further traverses the rejection by arguing that it requires only routine experimentation to identify a novel gene or coding region and to identify a novel mutation or polymorphism that is associated with bipolar disorder and that undue experimentation is not required. It is asserted that Applicants have narrowed the region of chromosome 18 that is linked with bipolar disorder and that this alone is sufficient to enable the identification of a gene, coding region, mutation or polymorphism linked to bipolar disorder. These arguments have been fully considered but are not persuasive. Narrowing the region to only 8.9 cM does not provide a more definitive and specific characterization of a gene, mutation or polymorphism that is associated with bipolar disease. The disclosure of a narrower region, while limiting to some extent the amount of research that must be must be done, does not in fact remove the unpredictability associated with identifying a new gene, mutation or polymorphism correlated. Again, there is no disclosure in the specification of a gene, mutation or polymorphism associated with bipolar disorder. The specification provides only the steps of the research project which one could practice in the hope of eventually identifying a gene, mutation or polymorphism associated with bipolar disorder. The fact that the region now consists of 8.9 cM, rather than the larger previously defined region of 18q21-q23, does not ensure a reasonable expectation of success that a gene, mutation or polymorphism associated with a bipolar disorder can be identified without undue experimentation.

Applicants argue that while the steps of the invention may be time-intensive and labor-intensive, this does not mean that they require extensive experimentation. This argument has been fully considered but is not persuasive. It is agreed that methods are

known in the art for comparing gene sequences and that it would be within the skill of the art to compare the stated 18q regions of affected and unaffected individual. However, the claims are not limited to such methods. Rather, the claims are drawn to methods for **identifying at least one human coding region/gene, including a mutated or polymorphic variant thereof, which is associated with bipolar disorder.** The claims require the steps of identifying the position of a coding region or gene in a region of approximately 8.9 or 15.2 million bp - a region that potentially includes hundreds of genes. If the claim was limited to only the step of searching within the stated region for the position of a gene, then such a claim may in fact be enabled because it is within the skill of the art to search and try to find a gene. However, such methods would also be obvious since the methodology of searching for genes is known, as were methods of searching for genes in chromosome 18q21-q23. But, the claims are not limited to only methods of trying to identify the position of any gene within D18S68-D18S979. Rather, the claims require determining the position of a gene that is associated with bipolar. It is not a matter of simply determining the position of any gene – but a matter of determining the position of a particular gene which meets the criteria of being associated with bipolar. Further, the claims require a step of comparing the sequences of an affected individual and a control individual in order to identify a coding region/gene or mutated or polymorphic variant thereof associated with bipolar disorder. This step is not limited to a more general methodology of merely comparing sequences and searching and trying to identify any sequence variation. Again, such methodology would clearly be obvious. What is not obvious and what is not routine, is the ability to

perform these method steps to identify a coding region or gene or mutated or polymorphic variant thereof that is associated with bipolar.

Further, Applicants interpretation of what constitutes routine experimentation is clearly in great contrast to what those of skill in the art view as "routine experimentation." It is maintained that it is not simply a matter of routine experimentation to identify a novel gene or mutation or polymorphism associated with bipolar disease. The extensive amount of experimentation that is discussed in the cited references provides evidence of this fact.

In particular, Applicants previously cited WO 02/101044 (Del-Favero et al.; co-inventor of the present application) as teaching methods for trying to obtain a gene associated with bipolar using the same experimental procedures set forth in the present application. Applicants admitted that Del-Favero determined that "(n)o alleles, genotypes or haplotypes were found to be significantly associated with bipolar disorder, indicating that NCAG1 itself is not a candidate bipolar gene." The teachings of Del-Favero emphasize the unpredictability associated with identifying a novel gene or mutation linked with a disorder. As set forth by Del-Favero et al, even after a region has been identified that is linked to bipolar disorder and even with knowledge of the experimental techniques (which were actually known in the art far prior to Applicants application), the ability to identify a gene or mutation linked with bipolar disorder remains unpredictable. The WO 02/101044 document provides evidence that even the co-inventor of the instant application, following the same methodology as set forth in the present claims, was unable to identify a mutation or polymorphism associated with BP.

Also, as discussed in the above rejection, the teachings of Goossens support the unpredictability in the art of identifying a marker in the D18S69-D18S979 region that is associated with bipolar since Goossens teaches that the CAG and GTG triplets between D18S69-D18S979 are not involved in BP disorder. Del-Favero also teaches no alleles, genotypes or haplotypes of a gene within the D18S69-D18S979 region, NCAG1, are associated with BP disorder. These results emphasize that only through trial-by-error experimentation can one identify a repeat that is associated with bipolar. That is, knowledge that a region is linked to bipolar disorder does not allow one to immediately envision or obtain without undue experimentation, repeats (mutations or polymorphisms or other markers) that are associated with bipolar disorder.

The response argues that Applicants concur with the statement "that not all polymorphisms present between D18S68-D8S979 will necessarily be linked to bipolar disorder, but successful use of the invention does not require that each polymorphism be so linked. Routine practices in molecular biology will readily allow one of ordinary skill in the art to do the analysis necessary to determine whether a polymorphism in the D18S69-D18S979 region is indeed associated with bipolar disorder." This argument has been fully considered but is not persuasive. The claims are not limited to methods in which additional analysis steps are performed to distinguish between polymorphisms associated with bipolar disorder and polymorphisms not correlated with bipolar disorder. Rather, the claims recite only two steps: a first step of determining the position of a gene; and a second step of detecting differences in the coding region/gene of an affected and unaffected individual. Based only on these steps, one concludes that any

difference in the coding region/gene of the affected individual versus the unaffected individual indicates that the coding region, gene, mutation or polymorphism is one which is associated with bipolar disorder. Accordingly, Applicant's arguments do not reflect the claims as written since the claims do not recite what appear to be critical process steps of analyzing the sequence variations and trying to determine which of the variations constitutes a gene, coding region, mutation or polymorphism that is associated with bipolar disorder.

Applicants state that the results in the specification "were the result of a replication study to test linkage with chromosome 18" and cite page 3 of the specification in support of this argument. Applicants thereby conclude that the Lander reference does not support the enablement rejection. First, it is again noted that the Office action did not require that Applicants provide a p value for the study. Secondly, page 3 of the specification states only that "In an independent replication study, the present inventors tested linkage with chromosome 18 markers in 10 Belgian families with bipolar proband. To localize causative genes the linkage analysis or likelihood method was used in these families." Since Applicants prior response and declaration argued the significance of the p value, it is again pointed out that the response and declaration did not clarify how this p value was obtained – i.e., the basis for concluding that the lod score of 2.0 is equivalent to a p value of 0.01.

Applicants argue that "because the specification demonstrates a significant genetic linkage between the relevant region of human chromosome 18 and bipolar disorder, Applicants submit that there would be a high expectation of success that an

analysis of the region identified by Applicants, would lead to the identification of one or more polymorphisms and genes associated with susceptibility to disease." However, Applicants have not established that all markers in the "relevant region" are associated with BPII or other bipolar disorders. The results set forth in the specification indicate that several of the markers in the claimed region were determined by Applicants to NOT be significantly linked to BPII. For instance, for "Model 1," the following markers in this region did not have lod scores that would be viewed as significant: the lod score for D18S68 and D18S346 was –0.19; the lod score for D18S969 was 1.40; the lod score for D18S979 was –0.18; the lod score for D18S61 was –0.21. That is, the claims include the analysis of the region between markers D18S68 to D18S113. However, Applicant's data establishes that the markers in this region, namely D18S68, D18S346 and D18S969 were not linked with BPII. Further, the claims encompass the analysis of a region that spans markers D18S79 to D18S61. However, the markers in this region, D18S979, D18S817 and D18S61 had lod scores of –0.18, -0.19, and –0.21, respectively and thus were not linked with BPII in this proband. Therefore, the disclosure in the specification of 3 markers having of a lod score of 2.01 (in "Model 1") – the adjacent markers of D18S113, D18S876 and D18S477, is not sufficient to enable one of skill in the art to identify a gene, coding region, mutation or polymorphism in the complete region flanked by D18S68 to D18S979 or D18S60-D18S61 without undue experimentation. Even if the information obtained using Model 1 was not considered and only the information obtained from model 3 was considered, the data from this

model does not establish a linkage between BPII and the markers D18S51, D18S69, D18S346, D18S979, D18S817, and D18S61 (see page 31 of the specification).

Further, no data is provided for the markers between D18S60 and D18S68 or between D18S61 and D18S979. The specification (e.g., Figure 14) discusses only the region between D18S68 and D18S979 as being a "BP candidate region." There is no evidence to support the conclusion that the regions outside of D18S68- D18S979, extending to D18S61 and D18S60 are associated with BP.

At page 9 of the response, Applicants assert that now that they have identified a region in the genome associated with bipolar, one can use this information to **"search for"** polymorphic variants and genes associated with bipolar. However, as set forth in *Brenner v. Manson,* 383 US 519, 535-536, 148 USPQ 689, 696 (1966), "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." In the present situation, Applicants have not identified a single coding region or gene or a single mutation or polymorphism associated with bipolar disorder. Applicants have identified a narrower region of the human genome which might include a gene, mutation or polymorphism associated with bipolar disorder. However, the specification does not disclose any genes, coding regions, mutations or polymorphisms associated with bipolar. Rather, the specification provides only an invitation to researchers so that they may go out and seek the novel aspects of the claimed invention – i.e., an invitation to try to identify a gene, coding region, mutation or polymorphism associated with bipolar disorder.

Lastly, the response does not address the rejection to the extent that it is based on the unpredictability of extrapolating the results obtained with one family having a BPII proband to other types of bipolar disorders (BP-I, SAD-M, and unipolar major depressive disorder). As discussed above, the different types of bipolar disorders have different symptomologies and are believed to be genetically distinct and the teachings of De bruyn indicate that the 18q markers are not linked to bipolar in a MAD22 BPI proband. No evidence or scientific arguments have been presented to establish that the results obtained with one family having a BPII proband can be extrapolated to all other types of bipolar disorders.

Accordingly, the above rejection is maintained because while the specification has taught one of skill in the art how to search in general for a gene, coding region, mutation or polymorphism, the specification has not adequately taught one of skill in the art how to identify a gene, coding region, mutation or polymorphism associated with any bipolar disorder without undue experimentation.

The following are new grounds of rejection:

3. Claims 2-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The specification as originally filed does not appear to provide support for the concept recited in amended claims 2-5 of a method for identifying the position of a

"control coding region/gene." The specification (page 10) discusses methods in which DNA from a "control individual" is compared to DNA from an affected individual. Further, page 20 of the specification discusses methods in which a sample of DNA from "is screened for any deviation from a control (normal) DNA." However, the specification does not particularly refer to control coding regions and genes. Since this phrase is not clearly defined in the specification, it has been given its broadest most reasonable interpretation as including coding regions and genes which control gene expression or other biological activities, as well as coding regions/genes that are present in the genome of control (normal) subjects. The teachings in the specification regarding methods of comparing the DNA from an affected individual to that of a control (normal) individual, does not provide support for the distinct concept of a method of identifying the position of a "control coding region/gene" and identifying differences between the "control coding region/gene" and the coding region/gene of an individual afflicted with a bipolar disorder.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 2-5 are indefinite over the recitation of "control coding region/gene." This phrase is not clearly defined in the specification and there is no art recognized definition for this phrase. It is unclear, for example, as to whether control coding regions or genes

are intended to refer to sequences which control the expression or activity or another gene or protein or refer to sequences obtained from a normal, unaffected individual. In the former case, it is unclear as to what would constitute a control region or gene within the D18S60-D18S51 region. Accordingly, one of skill in the art cannot determine the meets and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3 are rejected under 35 U.S.C. 102(e) as being anticipated by Freimer et al (U.S. Patent No. 6,136,532).

The following rejection is based on the interpretation that the claims as broadly written include methods comprising the steps of i) identifying the position of a coding region or a gene within D18S68 to D18S979 or any portion thereof, and ii) detecting any difference in the sequence of the identified coding region or gene as compared to that from an individual affected with a bipolar disorder, wherein it is a property of step ii) that this step of detecting any difference in the coding region or gene necessarily results in the identification of a coding region, or gene, or mutated or polymorphic variant thereof associated with BP. As noted in the MPEP 211.02, " a preamble is generally not

accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone." Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give "life, meaning and vitality" to the claim, "then the preamble is of no significance to claim construction because it cannot be said to constitute or explain a claim limitation". Therefore, the claim language of "for identifying at least one human coding region/gene, including mutated or polymorphic variants thereof" is considered to be a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. Further, the final clause of "wherein a difference in the coding region/gene...identifies the coding region/gene or mutated or polymorphic variant thereof as associated with bipolar disorder" does not recite any additional active process steps, but simply states a characterization or conclusion of the results of the previously recited steps. Therefore, the "wherein" clause is not considered to further limit the method defined by the claims and has not been given weight in construction of the claims. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993) ("A 'whereby' clause that merely states the result of the limitations in the claim adds nothing to the patentability or substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003) ("A whereby clause in a method

claim is not given weight when it simply expresses the intended result of a process step positively recited.").

Freimer teaches methods comprising the steps of identifying the position of a coding region or gene; comparing the sequences of a coding region or gene from a bipolar affected individual and an unaffected (control) individual; and detecting differences in the identified coding region or gene of a bipolar affected individual and an unaffected individual (col. 18- 20). Freimer also teaches methods comprising the steps of obtaining YAC clones comprising sequences between genetic markers associated with bipolar disorder, comparing the sequences of corresponding YACs from affected and unaffected (control) individuals, and identifying differences in said sequences (see col. 19-20). The reference teaches the analysis of sequences and YACs containing sequences from the region of 18q22-q23. In particular, Freimer teaches the analysis of markers shown in Figure 6B (including the D18S61 marker) from related and unrelated BP-1 and unaffected individuals in order to "further narrow the BP-I susceptibility region" (see col. 17, lines 8-17). The reference (col. 19, lines 59-67 to col. 20, lines 1-10) states that "Genetic and physical data help to map the bipolar mood disorder gene to the 18q22-q23 region of chromosome 18...Narrowing down the region in which the gene is located will lead to sequencing of the bipolar mood disorder gene as well as cloning thereof. Further genetic analysis employing, for example, new polymorphisms flanking D18S59 and D18s476 as well as the use of cosmids, yeast artificial chromosome (YAC) clones, or mixtures thereof, are employed in the narrowing down process. The next step in narrowing down the candidate region includes cloning of the chromosomal region of

18q22-q23 including proximal and distal markers in a contig formed by overlapping cosmids and YACS." Since Freimer teaches the analysis of sequences and YACs from the 18q22-23 region, and sequences and YACs that contain the D18S61 marker, the method of Freimer is considered to be one that identifies a coding region (i.e., the position of coding sequences) between markers D18S68 and D18S979 (i.e., a region that includes sequences within 18q22-q23) and one that identifies the position of a control coding region in a YAC clone that comprises any portion of human chromosome between D18S60 and D18S61 or D18S68 to D18S979.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freimer in view of De bruyn (cited in the IDS of October 21, 2004).

This rejection is based on the interpretation that the claims encompass the identification of a coding region or gene wherein the coding region or gene is specifically limited to one that is between markers D18S68 to D18S979 or D18S60 to S18S61. Further, as discussed in paragraph 5 above, the preamble of the claims and the final "wherein" clause are not considered to further limit the method defined by the claims and have not been given weight in construction of the claims.

The teachings of Freimer are presented above. In particular, Freimer teaches methods for the identification of a coding region and detection of differences in the sequence of a coding region from an individual having BPI, wherein the coding region comprises sequences from within the region of 18q22-q23. Freimer does not specifically teach the identification of coding regions and the detection of differences in coding region sequences wherein the coding regions consist of sequences from within the markers D18S69 to D18S979 or D18S60 to D18S61.

However, De bruyn teaches the analysis of nucleic acid sequences from a MAD31 family having a BPII proband (page 684). De bruyn states that the region of 18q21.33 to q23 flanked by markers D18S51 to D18S61 is linked to BP and may contain a candidate gene for BP disorder (see abstract, page 685, col. 2 and page 686, col. 2). It is noted that the D18S51 marker is within the region of D18S60 to D18S61 and the D18S69 and D18S979 markers are within the region flanked by markers D19S51 to D18S61.

In view of the teaches of De bruyn of linkage between the D18S51-D18S61 region and BPII and the teachings of De bruyn that this region is likely to contain a bipolar disorder gene, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Freimer so as to have analyzed the region of D18S51 to D18S61 or to have analyzed YACs containing sequences of this region for the presence of a coding region or gene and to have analyzed any identified coding regions or genes for the presence of sequence variations between BPII affected and non-affected individuals, in order to provide a method of screening for a gene associated with BPII and mutations or polymorphisms associated with BPII which could be used by investigators to further study the inheritance of and likelihood of being predisposed to BPII. It is noted that since the D18S51 to D18S61 region contains sequences from within D18S68 to D18S979 and from within a portion of D18S60 to D18S61, analysis of the complete D18S51 to D18S61 region allows for the identification of a coding region or gene within D18S68 to D18S979 and from within a region comprising a portion of D18S60 to D18S61.

.6. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Freimer and De bruyn, as applied to claims 1-3 above, and further in view of Cohen (Nature. 1993. 366: 698-701) and CEPH-GENETHON YACS (1995; available at url: <cedar.genetics.soton.ac.uk/ldb/chrom18/c1>).

The teachings of Freimer in view of De bruyn are presented above. The combined references do not specifically teach analyzing the YAC clone 961_h_9 or 907_e_1 for the presence of a coding region or gene.

However, Freimer (col. 17) teaches that "YAC clones (with inserts averaging about 750 Kb of human genomic DNA) that span the 18q22-q23 region have already been identified by the CEPH/Genethon consortium (Cohen et al., 1993) and are publicly available. Freimer teaches that such publicly available YACs can be used to narrow down the region containing a BP locus and to screen for possible candidate genes within the locus.

Cohen teaches a YAC library comprising sequences from human chromosome 18, as well as from other human chromosomes. The reference teaches the results of physical mapping of the YAC clones and provides information regarding the location of the YAC clones and the insert size of each clone. The CEPH-Genethon consortium web site (1995) discloses particular YACs within the 18q21-23 region. In particular, CEPH-Genethon discloses the 18q YAC clones 961_h_9, corresponding to marker D18S797 and 907_e_1, corresponding to marker D18S726.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have further modified the method of Freimer so as to have specifically analyzed YACs 961_h_9 and 907_e_1 for the presence of coding sequences and to have compared the sequences of these YACs with sequences from BPII affected individuals because these YACs comprise sequences within the region identified by De bruyn as being linked to BPII and therefore would provide an effective source of YAC clones to screen for a BPII associated gene.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

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